REMARKS

Claims 41-70 were pending prior to this Response. By the present communication, claims 51-55 have been cancelled without prejudice and claims 41, 64 and 68 have been amended to describe Applicant's invention with greater particularity. These amendments add no new matter, the amended claim language being fully supported by the Specification and original claims. Applicant submits that the claim amendments do not narrow the claims in any way within the meaning of Festo Corporation v. Shoketsu Kinzoku Kogyo Kabushiki Co. Ltd., a/k/a SMC Corporation and SMC Pneumatics, Inc. 234 F.3d 558, 51 U.S.P.Q. 2d 1959 (Fed. Cir. 2000). Accordingly, claims 41-50 and 56-70 are currently pending and under consideration.

The Objection to the Specification

Applicant traverses the objection to the Specification as allegedly failing to provide proper antecedent basis for the subject matter of claims 41 and 44-54 under 37 C.F.R. 1.75(d)(1) and MPEP § 608.01(o). With regard to the Examiner's objection to the phrase "mutagenesis in directed evolution" in claim 41, claim 41 has been amended to delete the phrase "mutagenesis in directed evolution," thus overcoming the grounds for the objection to claim 41. With regard to the Examiner's objection to claim 46 due to Applicant's alleged failure to complete the phrase "kb in size", by the present communication claim 46 has been amended to insert "kb in size", which was inadvertently omitted.

With regard to the rejection of claims 44-55 over the recitation of genomic DNA in various specific sizes that are allegedly not disclosed in the Specification, Applicant submits that

the Specification discloses that DNA inserts up to about 40 kb in size can be used in the invention methods (Specification at page 30, line 12). This recitation of appropriate size includes the specific sizes recited in claims 44-50. Consequently claims 44-40 have not been amended. Claims 51-55, which recite DNA in sizes larger than about 40 kb in size, have been cancelled without prejudice.

In view of the above amendments, Applicant respectfully requests reconsideration and withdrawal of the objection to the Specification.

The Rejection Under 35 U.S.C. § 102(e)

Applicant traverses the rejection of claims 41-70 under 35 U.S.C. § 102(e) as allegedly being anticipated by Thompson et al. (U.S. Patent No. 5,824,485; hereinafter "Thompson"). The invention methods for obtaining a desired bioactivity or biomolecule, as defined by amended claim 41, distinguish over the disclosure of Thompson by requiring "creating a DNA library comprised of DNA molecules obtained directly from an environmental source; introducing at least one mutation into a DNA molecule from said library to create a mutagenized DNA molecule; and screening to select a desired bioactivity or biomolecule containing a mutation." The term "directly" as used in claim 41 signifies that the DNA obtained from the environmental source is obtained without culturing the organisms to obtain isolates and without processing the DNA to select preferred DNAs or related DNAs so as to create a library characterized by a particular pre-selected characteristic. Applicants illustrate this procedure on page 6 of the Specification and in Example 1, wherein the ISOQUICK™ nucleic acid extraction kit and procedure is used to obtain substantially all DNA from the "exterior surface of a whale bone found at 1240 meters depth in the Santa Catalina Basin during a dive expedition" (Specification,

page 15). The organisms are not cultured and the DNA obtained by extraction is placed directly into a library (i.e., without pre-treatment to select preferred DNAs or related DNAs).

Thompson fails to disclose each and every element of the claimed invention. For example, Thompson fails to disclose placement of the genomic DNA extracted from environmental samples "directly" into a library. In fact, section 5.3.6 of the reference (relied upon by the Examiner as anticipating the present invention) only describes purification of nucleic acids from soil and does not teach or suggest formation of a library *"directly"* from such purified DNA for into a DNA library for mutation and screening.

In fact, when the reference is read "as a whole" in accordance with the statute, Thompson discloses a method wherein extracted DNA is further pre-selected by a number of "pre-screening" techniques. For example, in Example 6.5 entitled "PRE-SCREENING OF MARINE GRAM (-)/*E. COLI* LIBRARY BY PLATE REPLICATION" the marine bacteria obtained from seawater are first screened to obtain gram-negative pigmented marine bacterial species, which were "tested prior to preparation of the DNA libraries to determine redundancy, and to help determine the array of pre-screens to be done on the completed libraries" (Col. 59, lines9-13). The DNA was first "quantified by visualization" and 5 μg DNA from each of the 40 selected species was pooled, packaged in λ phage, and incubated on ampicillin in master plates. Then the DNA was pre-screened on "a series of differential and/or selective media (e.g. siderophore detection media (DAS) or antimicrobial lawns" (Thompson, Col 60, lines 1-4). Then six clones that had been pre-selected in this manner were isolated on the basis of proving positive for starch digestion ability and for ability to inhibit growth of pathogenic bacteria (Thompson, Col. 60, lines 7-11). Clones that passed this pre-screening were then sequenced to determine those containing DNA sequences encoding proteins homologous to those in a polyketide synthesis

pathway and then further subjected to screening techniques, including multiplex PCR, to determine the cognate parental species (Thompson, Col. 60, lines 20-38).

Thompson discloses a number of other types of pre-screening tests used in preparation of combinatorial libraries. Thompson distinguishes the term "pre-screening" from "screening" by the following general statement: "The term "pre-screen" refers to a general biological or biochemical assay which indicates the presence of an activity, a compound or a gene of interest. The term "screen" refers to a specific therapy-oriented biological or biochemical assay which is directed to a specific disease or clinical condition, and employs a target" (Thompson, Col. 33, lines 28-33). Thompson's method is further characterized as follows:

> Pre-screens and screens for each library are chosen after comprehensive characterization of the host organism and, whenever possible, of the donor organisms. Assays in which the host organisms are positive are disqualified, while assays in which the donor organisms are positive are considered acceptable library pre-screens or screens.

(Thompson, Col. 34, lines 38-43). Thus, Applicants submit that Thompson fails to disclose formation of a DNA library "directly" from the environmental sample, for example, omitting the elaborate prescreening steps described by Thompson, and mutagenesis of one or more DNA molecules of the library to obtain a desired bioactivity or biomolecule.

In addition, Thompson fails to disclose Applicant's technique of "introducing a mutation" into a clone contained in a library obtained directly from the environmental source. The term "introducing a mutation" as used in Applicant's Specification and claims is described in the Specification as including such techniques as "error-prone PCR," "oligonucleotide directed mutagenesis," "assembly PCR," "sexual PCR mutagenesis," "*in vivo* mutagenesis," "cassette mutagenesis," "recursive ensemble mutagenesis," and "exponential ensemble mutagenesis,"

which are each described in detail in the Specification at pages 13-14. Thompson is absolutely silent regarding "mutagens" and "mutagenesis" of any type, much less mutagenesis of DNA contained in a library of clones "directly" obtained from an environmental sample (i.e., without culturing the organisms to obtain isolates and/or elaborate pre-screening).

Accordingly, Applicant respectfully submits that Thompson fails to disclose each and every element of claim 41, as would be required to establish anticipation under 35 U.S.C. § 102 (e) and reconsideration and withdrawal of the rejection are respectfully requested.

The Rejection under 35 U.S.C. § 103

Applicant respectfully traverses the rejection of claims 41-70 over claims Thompson in view of the state of the art as exemplified by Stemmer et al. (Stemmer et al. Proc. Natl. Acad. Sci. U.S.A. 1994, 91, 10747-10751; hereinafter "Stemmer") and Arnold et al. (as the Examiner does not state which reference by Arnold is intended, it is assumed for the purposes of this response that U.S. Patent No. 5,316,936 is intended; hereinafter "Arnold"). Applicant respectfully submits that the invention methods for obtaining a desired bioactivity or biomolecule, as defined by amended claim 41, distinguish over the combined disclosures of Thompson in view of the art as exemplified by Stemmer and Arnold by requiring "creating a DNA library comprised of DNA molecules obtained directly from an environmental source; introducing at least one mutation into a DNA molecule from said library to create a mutagenized DNA molecule; and screening to select a desired bioactivity or biomolecule containing a mutation."

The remarks above distinguishing the invention methods over the disclosure of Thompson apply equally here. Thompson neither teaches nor suggests formation of a library

directly from an environmental sample and mutagenesis of such a library to obtain a desired bioactivity or biomolecule. Applicant respectfully submits that the Examiner has fashioned the rejection by "picking and choosing" a passage of Thompson that describes DNA extraction from an environmental sample and has failed to consider the reference "as a whole" by ignoring the massive amount of disclosure pertaining to preparation of isolates and pre-screening in the reference that teaches away from Applicant's invention. In addition, Applicant submits that Thompson provides no motivation to modify the disclosed methods by omitting the culturing and/or pre-screening steps to obtain the library "directly" from the environmental sample because Thompson teaches that the pre-screening steps are important to reduce the number of clones to be screened as a means of improving the likelihood that screening will yield a molecule having the desired properties (See for example, Section 5.1.6 of Thompson). Thus, Applicant submits that Thompson neither teaches nor suggests the invention methods as defined by amended claim 41.

Moreover, Applicant respectfully submits that the state of the art as represented by Stemmer and Arnold does not overcome the deficiencies of Thompson for suggesting the invention methods under 35 U.S.C. § 103. The Examiner relies upon Arnold as disclosing a method of obtaining mutants of subtilisin using random mutagenesis of a gene encoding the enzyme by various methods of mutagenesis (Office Action, page 6). However, like Thompson, Arnold neither teaches nor suggests preparation of a library "directly" from DNA obtained from an environmental sample. Instead, Arnold discloses mutagenesis of one or more individually isolated or synthesized subtilisin-encoding genes. Applicant respectfully submits that Arnold has nothing to do with the idea of mining the diverse population of organisms that are to be found in rare environmental samples and, furthermore, Arnold neither teaches nor suggests formation of a library directly from any environmental sample as the term "directly" is used in Applicant's claims.

Similarly, Applicant respectfully submits that Stemmer fails to overcome the deficiencies of Thompson, either alone or in combination with Arnold. Like Thompson and Arnold, Stemmer is silent regarding obtaining a desired bioactivity or biomolecule by creating a DNA library "directly" from an environmental source, introducing at least one mutation into a DNA molecule in the library and then screening to select a desired bioactivity or biomolecule containing a mutation. Instead Stemmer describes preparation of a library of fragments obtained by "digesting a large gene *obtained by PCR from a plasmid* with DNase I to a pool of random DNA fragments. These fragments were then reassembled into a full-length gene by repeated cycles of annealing in the presence of DNA polymerase as shown in Figure 2 (Stemmer, Materials and Methods, page 10747, Col 1). Thus, Stemmer fails to cure the deficiencies of Thompson for teaching or suggesting Applicant's invention.method of obtaining a DNA library directly from an environmental source.

Hence, Applicant respectfully submits that neither Stemmer in combination with Thompson, nor Stemmer and Arnold in combination with Thompson, is sufficient to establish *prima facie* obvious of the invention methods, as defined by amended claim 41. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

In view of the above amendments and remarks, reconsideration and favorable action on claims 41-50 and 56-70 are respectfully requested. If the Examiner would like to discuss any of the issues raised in the Office Action, Applicants' representative, Lisa A. Haile, J.D., Ph.D., can be reached at (858) 677-1456.

Respectfully submitted,

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Enclosure: Exhibit A

EXHIBIT A

Version with Markings to Show Changes Made

Please cancel claims 51-55 without prejudice.

Please amend claims 41, 64 and 68 to read as follows:

41. (Amended) A method for obtaining a desired bioactivity or biomolecule, comprising:

a) creating a DNA library comprised of DNA molecules obtained directly from an environmental source;

b) introducing at least one mutation into a DNA molecule from said library to create a mutagenized DNA molecule; and

c) screening [for] to select a desired bioactivity or biomolecule containing a mutation.

[whereby, if desired, biomolecules can be accessed from uncultivated organisms, and, if desired, improved thru mutagenesis in directed evolution]

64. (Amended) The method of claim 63, wherein the vector includes chromosomal, nonchromosomal or [syntheitic] synthetic DNA.

68. (Amended) The method of claim 41, further comprising:

[c]d) enriching for [a] one or more particular [organism or organisms] DNA molecules of interest.